UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,913	03/22/2004	Ashley J. Birkett	LOR-102.2 DVII (91645)	2511

24628 7590 08/04/2008

Husch Blackwell Sanders, LLP
Welsh & Katz
120 S RIVERSIDE PLAZA
22ND FLOOR
CHICAGO, IL 60606

EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
08/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,913	BIRKETT, ASHLEY J.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *101-109 and 116-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *101-109 and 116-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 28, 2008 has been entered.

2. Claims 101-109 and 116-118 are pending, and are under consideration in this Office action.

3. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the

advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Specification

4. The use of trademarks has been noted in this application, e.g. Superose ^{R}, [0094][0238], Bac-to-Bac^{TM}[0234], Alhydrogel^{TM} [0282][0283], and Montanide^{TM} [0285], etc. for example, throughout the text. Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objection

5. Claim 117 is objected to because of the following informalities: Claim 117, after (d)(ii), recites: "… said recombinant chimeric HBc protein molecules being more than are particles formed from an otherwise identical HBc chimer molecule ….". It is not clear what "… said recombinant chimeric HBc protein molecules being more (?) than are particles formed from an otherwise identical HBc chimer molecule…" Appropriate correction is required.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. (**Prior rejection-maintained**) The rejection of Claims 101-109 and 116-118 under 35 U.S.C. 103(a), as being obvious over Pumpens et al. (1995, in view of Zlotnick (1997) is **maintained** for the same reasons of record.

In response to Applicant's argument 1:

Applicant argues same arguments as that presented before: The cited references are not combinable. Specifically, no construct of Zlotnick contained heterologous epitope as claimed. Pumpens teaches insertion of heterologous sequences to enhance stability, which is an entirely different approach to Zlotnick and incompatible with the latter. As such, it is submitted that the two teachings are not appropriately combined in the Action and the rejection should be withdrawn (Remarks, p. 10).

8. Again, this argument is not convincing. "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). "The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

9. The cited Pumpens and Zlotnick references are combinable because they are all

related to the art of HBc particles. Both Pumpens and Zlotnick provide knowledge to one of ordinary skill in the art to how to construct stable HBc chimers. "When there is a design need or market pressure to solve a problem and there are a finite number of identified predictable potential solutions, a person of ordinary skill has good reason to pursue the known potential options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense". The Supreme Court decision in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007).

10. As discussed in the previous Office action dated June 22, 2006 (see e.g. Para 15-27), it was well known that HBc chimeras with c-terminal deletions (HBcΔ) does not "pack" viral RNA into HBc Particle, but HBcΔ particles were less stable than their full-length counterparts. Zlotnick clearly demonstrates that the addition of a cysteine residue to the c-terminal of HBcΔ results in enhanced stability of HBcΔ particles. One of ordinary skill in the art would have been motivated to combine the teachings of Pumpens and Zlotnick because "a person of ordinary skill has good reason to pursue the known potential options within his or her technical grasp". Therefore, Pumpens and Zlotnick references are combinable.

In response to Applicant's argument 2:

Applicant argues that Examples 22 and 23 of the specification that specifically relate to stability studies on assembled particles, and Table 20 shows that the particles containing an added C-terminal Cys residue exhibited unexpectedly greater immunogenicity that did similar particles lacking that C-terminal Cys (Remarks, p.11).

11. Applicant's argument is considered but found not persuasive. Examples 22 and 23 show, in analytical gel giltration analysis, that recombinant HBc V12.Pf1(C17A)C150, which has c-terminal Cys, is more stable than recombinant HBc V12.Pf1(C17A), which does not have c-terminal Cys. However, this result is not unexpected because it is consistent with the teachings of Zlonick. Zlotnick teaches that C-terminal Cys can stabilize HBcΔ. Zlotnick shows that the Cp*150 capsid, which is Cys C-terminally stabilized HBcΔ, is more stable than Cp*149, which is HBcΔ without the C-terminal Cys. Zlonick used SDS/PAGE gel and size exclusion chromatograph analyses (see Figure 2a and 2b, right column 9557) to teach that Cp*150 forms disulfide dimers at pH 7.5 and 9, but Cys-free Cp*149 does not. Zlotnick has also shown that the Cp*150 capsid is resistant to dissociation by 3.5 M urea, suggesting that disulfide bond formation by Cp*150 can promote capsid assembly (Results and Discussion, paragraph 1 and 2, p. 9558). Using cryo-electron microscopy, Zlotnick shows that Cp*150 capsid has well defined densities (right col. p.9559-p.9559, and Figure 4d-f). As a result, Zlotnick clearly teaches that HBcΔ with C-terminal Cys is more stable than HBcΔ without C-terminal Cys. In view of the teachings of Zlotnick, one of ordinary skill in the art would recognize that Applicant's result is expected because they are consistent with teachings of Zlotnick. It is also expected that stable HBc particle is more immunogenic than disassociated HBc because HBc particles maintain complete epitopes, especially conformational epitopes.

12. More importantly, Applicant's unexpected result is not commensurate in scope with the claims. The claims encompass a huge genus of all recombinant chimeric HBc containing a C-terminal Cys, wherein the HBc contains 0-100 heterolous sequence at its N-,C- or/and its immunogenic loop, wherein the HBc contains 5% substituted amino acid

residues compared to a sequence of SEQ ID NO:246-251. Examples 22 and 23 show that recombinant HBc V12.Pf1(C17A)C150, which has C-terminal Cys, is more stable than recombinant HBc V12.Pf1(C17A), which does not have C-terminal Cys. This result is not commensurate in scope with the claims. Therefore, applicant's arguments of unexpected results have not been found convincing.

In response to Applicant's argument 3:

13. Applicant provided following arguments in Remarks p. 12 regarding the teaching of Zlotnick:

> The Action first discusses the alleged contribution of the Zlotnick manuscript. The premise that Zlotnick teaches the *C*-terminal cysteine can stabilize an HBc chimer molecule as recited in the claims here cannot be agreed with. This premise is inconsistent with the statements and data provided therein by Zlotnick.
>
> For example, Zlotnick explicitly states: "[p]urified Cp*149 and Cp*150 assemble into capsids under the same conditions as other constructs, with or without DTT. These capsids were *indistinguishable* (emphasis added) by negative staining electron microscopy and sedimentation on sucrose gradients." (See page 9558, column I, paragraph 1, Results and Discussion section.) As a second example, Zlotnick reports: "[a]t a resolution of ~20A, the outer surface of the Aull- labeled [monomaleimidyl-undecagold-labeled] Cp*150 capsid is indistinguishable (emphasis added) from those of unlabeled Cp147 and Cp183 capsids, (cf. Fig. 4 Top)." (See page 9558, column 2, and paragraph 1) These facts would lead one skilled in the art to conclude that *C*-terminal cysteines are not important for HBcA capsid formation or stability.

14. Applicant's citations of Zlotnick are not complete, and the conclusion is misleading. The following is the complete citation of Zlotnick from page 9558, column 1, paragraphs 1 and 2, Results and Discussion section):

> [P]urified Cp*149 and Cp*150 assemble into capsids under the same conditions as other Cp constructs (10, 15), with or without DTT. These capsids were indistinguishable by negative staining electron microscopy and sedimentation on sucrose gradients (data not shown). When reduced CP*150 capsids were stored without DTT for 2 days, >90% of the protein oxidized to form disulfide-bonded dimers (Fig. 2 *a*). These bonds stabilize the quaternary structure of the capsid, as attested by the observation that oxidized Cp*150 capsids—unlike CP*149 capsids or reduced Cp*150 capsids—are resistant to dissociation by 3.5 M urea (Fig. 2 *b*). Knowledge of the location of residue 150 (see below) indicates that this disulfide bond links two dimers (Fig. 1 *b*) and is

distinct from the intradimeric disulfide observed in Cp proteins with native cysteines (16, 25).

Generally, when Cp proteins are stored in a low ionic strength, high pH buffer they do not polymerize (10). However, when stored in this buffer without DTT, Cp*150 dimers assemble into capsids, as determined by negative stain electron microscopy and analytical ultracentrifugation. A high proportion of the protein in these capsids is disulfide-bonded (Fig. 2 *a*). These data show that disulfide bond formation by Cp*150 can promote capsid assembly. Without disulfide formation, higher-order structures do not accumulate in storage buffer, i.e., the rate for dissociation is greater than the rate of association. Formation of these disulfide bonds stabilizes complexes against dissociation. Thus, under these conditions, Cp polymerization appears to involve an equilibrium between subunits, assembly intermediates, and capsids (36). We also note that, in capsids, the cysteine 150 residues from adjacent subunits must be close enough to one another to form a covalent bond, a distance of 4.6–7.4 Å between α carbons (37). (Underline emphasis added by the examiner)

15. In view of teachings recited above, one skilled in the art would conclude that Zlotnick explicitly teaches that Cp*150, which contains a *C*-terminus cysteine, is more stable than Cp*149, which does not contain a *C*-terminus cysteine. These facts would lead one skilled in the art to conclude that *C*-terminal cysteines are important for HBcA capsid formation and stability.

In response to Applicant's argument 4:

Applicant asserts from Figure 2a of Zlotnick that the polyacrylamide gel shown therein depicts disulfide bonded *dimers* **not HBcA core protein capsid particles**. Those capsids are the entities recited in the claims to have enhanced stability. (Remarks 12-14). Applicant argues that nothing in Zlotnick has shown the capsids behave like dimers, See Remarks p22-23.
Applicant asserts "The present claims recite the stability of the particles assembled from those monomers and dimers. As such, a disclosure concerning the stability or lack thereof of dimers or monomers neither teaches nor suggests anything of relevance to the claimed subject matter whether taken alone or with any other disclosure" (Remarks, Para 1, p. 13).

16. This argument is not convincing because while targeting Zlotnick Fig. 2 alone, Applicant again ignores the teachings in Zlotnick specifically related to **HBcA core**

protein capsid particles. Specifically, Zlotnick shows capsid protein in Figure 2(b). Zlotnick teaches in Fig. 2(b) as recite: "(b) size exclusion chromatography of **capsid** protein (particles) after exposure to 3.5 M urea. Samples are oxidized Cp*150 (solid line), Cp*150 with 130 mMDTT (dashed line) and Cp*149 (dotted line)". See Description of Fig. 2, right col. p. 9557. Here, oxidized Cp*150 is polymerized capsid, Cp*150 with 130 mM DTT is reduced Cp*150, containing both polymerized and disassociated capsid particles. Thus, Figure 2b simply shows that Cp*150, shown as single peak of capsid polymer, is more stable than Cp*149, shown as two peaks of polymerized and disassociated capsid.

17. Moreover, in Figure 3, Zlotnick teaches cryo-election microscopy of Cp149, Cp*150 capsid. In Figure 4, Zolonick shows image reconstruction of T = 4 HBV capsids. In Fig. 1b, Zlotnick teaches Cp150 dimers connected by a disulfide bond between Cys-150 residues (See e.g. 1b, Description of Fig. 1b, and page 9558, col. 1, paragraphs 1 and 2, Results and Discussion section). These figures clearly show that Cp*150 forms capsid particles assembled from HBc dimers!

In response to Applicant's argument 5:

18. Applicant further asserts that Cp150, which is HBc containing C-terminus Cys, failed to associate into dimer or has readily disassociated as shown in Zlotnick's Fig. 2a lane 6 and lane 7, suggesting Cp150 is not stable. (Remarks p. 14-16).

19. This argument is not relevant to the claims. Applicant argues the limitations that are not in the claims. The instant claims are directed to a genus of immunogenic particles that are comprised of a plurality of recombinant chimeric HBc protein molecules have a

length of up to about 515 amino acids...". The instant claims do not require being absence of HBc monomer. Zlotnick shows in Fig. 2a that the vast majority of Cp150, which contains no C-terminus Cys, is polymers (See lanes 6 and 7), while Cp149, which contains no C-terminus Cys, is monomers (See lane 5). Thus, Zlotnick shows that Cp150 is a polymerized HBc molecule, which meets the claim limitation.

20. Furthermore, Fig. 2b shows that Cp*150, shown as single peak of HBc polymer capsid, is more stable than Cp*149, shown as two peaks of polymerized and disassociated capsid. Thus, Zlotnick has demonstrated that C-terminus-Cys enhances stability of HBc.

Remarks

21. No claim is allowed. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Bo Peng/
Patent Examiner
July 31, 2008

/Bruce Campell/

Supervisory Patent Examiner, Art Unit 1648